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Original Research

Quality of life in metastatic pancreatic cancer patients receiving liposomal irinotecan plus 5-fluorouracil and leucovorin

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Abstract ***Background:*** The NAPOLI-1 study (NCT01494506) reported that liposomal irinotecan plus 5-fluorouracil and leucovorin (nal-IRI+5-FU/LV) improved overall survival vs 5-FU/LV with manageable toxicity in patients with metastatic pancreatic adenocarcinoma previously treated with gemcitabine-based therapy. Yet, clinicians need treatment strategies that

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Drug combinations, antineoplastic; Neoplasm metastasis; Pancreatic neoplasms; Quality of life

also maintain the patient's health-related quality of life (HRQOL). Here, we report the HRQOL data.

Methods: Patients completed the European Organisation for Research and Treatment of Cancer QOL core questionnaire C30 (EORTC QLQ-C30) at baseline, every 6 weeks, and at 30 days after discontinuation of study treatment. Patient-reported outcomes (PROs) were scored according to EORTC guidelines. nal-IRI+5-FU/LV HRQOL was compared with 5-FU/LV. The PRO population comprised intent-to-treat patients who completed baseline and at least one subsequent assessment on the EORTC QLQ-C30. Data were also analysed for missingness.

Results: Of 236 patients in the intent-to-treat population, 128 (54.2%) comprised the PRO population (71 in the nal-IRI+5-FU/LV arm; 57 the in 5-FU/LV arm). Of the remaining 108 patients (45.8%) not included in the PRO population, most progressed rapidly, making participation difficult. Median change from baseline was ≤10 points at weeks 6 and 12 in global health status or functional and symptom scale scores, except for fatigue, which deteriorated by 11.1 points with nal-IRI+5-FU/LV but did not change vs 5-FU/LV. The proportion of patients whose HRQOL improved or deteriorated was not significantly different between the arms.

Conclusion: In the NAPOLI-1 study, HRQOL was maintained with nal-IRI+5-FU/LV in patients with metastatic pancreatic adenocarcinoma previously treated with a gemcitabine-based regimen, while survival was significantly extended.

1. Introduction

Pancreatic ductal adenocarcinoma is an aggressive disease with poor 5-year survival [1–3]. It is currently the third and fourth leading cause of cancer-related death in the United States and Europe, respectively [4,5] and is predicted to become the second leading cause of cancer-related death in the United States by 2030 [6]. At diagnosis, only 20% of patients present with resectable, potentially curable disease [7].

Few first-line chemotherapy regimens exist for metastatic pancreatic ductal adenocarcinoma (mPDAC) [8–10]. For patients with well-preserved performance status (PS), guidelines recommend folinic acid/leucovorin, 5-fluorouracil, non-liposomal irinotecan and oxaliplatin (FOLFIRINOX) and combination of gemcitabine and nab-paclitaxel [8,9]. For less fit patients, gemcitabine monotherapy or other gemcitabine-based combinations may be used [8,9]. Recently, the US Food and Drug Administration, European Medicines Agency and other regulatory bodies approved liposomal irinotecan (nal-IRI; Onivyde®; MM-398) in combination with 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) for patients with mPDAC who have progressed following gemcitabine-based therapy.

nal-IRI is a liposomal formulation of the topoisomerase I inhibitor, irinotecan. Liposomal encapsulation protects irinotecan from premature hepatic conversion to the active metabolite SN-38, resulting in extended availability and enhanced intratumoral drug deposition [11–13]. After deposition, phagocytic cells convert nal-IRI to SN-38, increasing its activity by approximately 100- to 1000-fold [11–14].

The NAPOLI-1 study was a global phase III, randomised, open-label, multicentre study (NCT01494506) that tested nal-IRI monotherapy or nal-IRI+5-FU/LV vs 5-FU/LV alone in patients with mPDAC previously treated with gemcitabine-based therapy. nal-IRI+5-FU/LV led to significant improvements in median overall survival (OS; an increase by 45% [6.1 months vs 4.2 months]; hazard ratio 0.67; 95% CI 0.49–0.92; $P = 0.01$]). nal-IRI+5-FU/LV also significantly improved a number of secondary endpoints, including progression-free survival [15]. A recent updated analysis confirmed this survival benefit [16]. Side-effects reported for the nal-IRI+5-FU/LV combination were manageable and typically reversible; the most frequent grade ≥3 adverse events included neutropenia, diarrhoea and vomiting [15]. Although adverse events led to dose reductions more often in the nal-IRI+5-FU/LV arm (33%) than in the 5-FU/LV arm (4%) [15,16], incidence of adverse event-related treatment discontinuation was similar between the nal-IRI+5-FU/LV (11%) and 5-FU/LV (7%) arms. Because of these results, guidelines now recommend the nal-IRI+5-FU/LV combination for patients who have progressed following gemcitabine-based therapy [8–10,17].

Advanced pancreatic cancer is often associated with abdominal pain, appetite and weight loss and decreased functional status, symptoms that compromise patient health-related quality of life (HRQOL) [8]. In addition, chemotherapy—the standard of care in this setting—is often associated with treatment-emergent toxicities that further affect HRQOL [8,18]. Thus, new mPDAC treatment strategies must both improve survival and preserve HRQOL [19]. Here, we explore the effects of the nal-IRI+5-FU/LV regimen on HRQOL.

2. Materials and methods

2.1. Study design and treatment

The NAPOLI-1 study design, methodology and inclusion criteria have been published previously [15]. The key inclusion criteria were a Karnofsky PS (KPS) score ≥70 and adequate haematological, hepatic and renal function. Patients were stratified by baseline albumin levels (≥40 g/L *vs* < 40 g/L), KPS (70 and 80 *vs* ≥ 90) and ethnic origin (white *vs* East Asian *vs* all others). Patients were randomised to nal-IRI+5-FU/LV combination therapy (nal-IRI 80 mg/m^2 [expressed as irinotecan hydrochloride salt, equivalent to 70 mg/m^2 irinotecan free base], subsequently LV 400 mg/m^2, then 5-FU 2400 mg/m^2 46-h infusion Q2 weeks [Q2W]), nal-IRI monotherapy (120 mg/m^2 nal-IRI Q3W) or a 5-FU/LV control arm (200 mg/m^2 LV, then 2000 mg/m^2 5-FU, 24-h infusion weekly for the first 4 weeks of each 6-week cycle). Patients routinely received supportive care according to local institutional standards as part of their trial participation, including granulocyte colony-stimulating factor prophylaxis if indicated.

2.2. HRQOL assessments

HRQOL was a secondary endpoint in the NAPOLI-1 study and was evaluated by the European Organisation for Research and Treatment of Cancer quality of life core questionnaire C30 (EORTC QLQ-C30). The EORTC QLQ-C30 has three independent domains: global health status, functional scales (physical, role, cognitive, emotional and social) and symptom/other scales (appetite loss, constipation, diarrhoea, dyspnoea, fatigue, insomnia, pain, nausea and vomiting and financial difficulty). Patients were asked to complete the EORTC QLQ-C30 at baseline (within 7 days of starting treatment), every 6 weeks thereafter, and 30 days after discontinuation of study treatment. On treatment days, the EORTC QLQ-C30 was completed prior to study drug administration.

The EORTC QLQ-C30 was scored according to EORTC guidelines [20]. The scores were standardised on a 0–100 scale by linear transformation of raw scores. For the functional scale or global health status, higher scores represent better functioning, whereas for the symptom scale, higher scores represent higher symptom burden [20]. A ten-point change in the EORTC QLQ-C30 was considered clinically meaningful [21,22]. For global health subscales and functional subscales, patients were categorised as improved (≥10% improvement *vs* baseline and remaining improved over baseline for ≥ 6 weeks), worsened (either died or had scores that worsened by 10% *vs* baseline), or stable (did not meet criteria for improved or worsened). Duration of improvement was the interval between the first date when the score improved ≥ 10% and the date when the score returned to baseline or lower.

Two types of missing data, namely domain non-response (a patient completed at least one but not all domains of the questionnaire at a particular time point) and unit non-response (a patient completed no domains for a particular time point), were analysed.

Patterns of missing data were also evaluated. Monotone (terminal) missingness is unit non-response followed by no subsequent completion of an EORTC QLQ-C30 domain during the treatment period. Monotone missingness occurs when a patient leaves the study and never returns, possibly because of death or study discontinuation [23]. Intermittent missingness is unit non-response followed by a complete (non-missing) domain at any subsequent time point during the treatment period. Intermittent missingness may occur when a patient misses a particular visit but returns at later scheduled visits [23].

2.3. Statistical analysis

The full analysis patient-reported outcomes (FPRO) population consisted of all patients in the intention-to-treat (ITT) population (all randomly assigned patients) who had completed at least one item of the EORTC

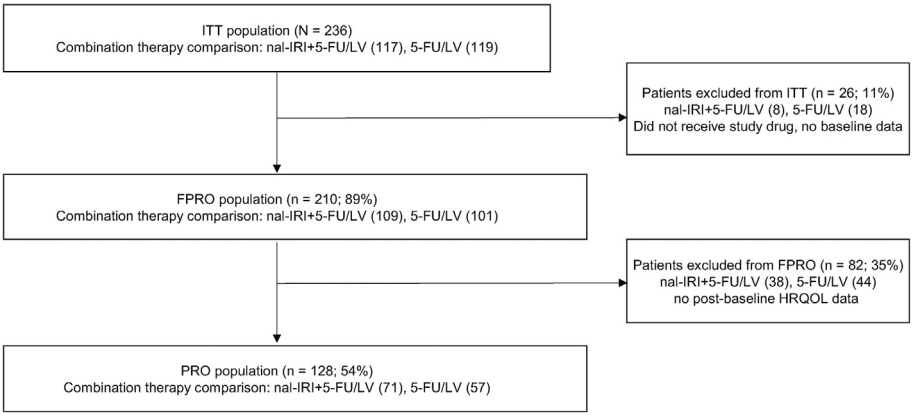


Fig. 1. Flowchart of patients in the combination therapy and control arms of the NAPOLI-1 study for HRQOL analysis. ITT, intention-to-treat; nal-IRI, liposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; FPRO, full analysis patient-reported outcome; PRO, patient-reported outcome; HRQOL, health-related quality of life.

Table 1
Baseline demographics and patient characteristics.

	PRO population (n = 128)		non-PRO population (n = 108)		ITT population (n = 236)	
	nal-IRI+5-FU/LV (n = 71)	5-FU/LV (n = 57)	nal-IRI+5-FU/LV (n = 46)	5-FU/LV (n = 62)	nal-IRI+5-FU/LV (n = 117)	5-FU/LV (n = 119)
Sex, *n* (%)						
Male	43 (60.6)	31 (54.4)	26 (56.5)	36 (58.1)	69 (59.0)	67 (56.3)
Female	28 (39.4)	26 (45.6)	20 (43.5)	26 (41.9)	48 (41.0)	52 (43.7)
Age, *years*						
Median	63.0	63.0	65.0	61.0	63.0	62.0
Range	41–81	41–80	45–80	34–79	41–81	34–80
Ethnic origin, *n* (%)						
Asian	22 (31.0)	16 (28.1)	12 (26.1)	20 (32.3)	34 (29.1)	36 (30.3)
Black or African American	3 (4.2)	1 (1.8)	1 (2.2)	2 (3.2)	4 (3.4)	3 (2.5)
White	42 (59.2)	39 (68.4)	30 (65.2)	37 (59.7)	72 (61.5)	76 (63.9)
Other	4 (5.6)	1 (1.8)	3 (6.5)	3 (4.8)	7 (6.0)	4 (3.4)
Karnofsky performance score, *n* (%)						
100	12 (16.9)	8 (14.0)	6 (13.0)	9 (14.5)	18 (15.4)	17 (14.3)
90	31 (43.7)	23 (40.4)	20 (43.5)	17 (27.4)	51 (43.6)	40 (33.6)
80	24 (33.8)	22 (38.6)	14 (30.4)	29 (46.8)	38 (32.5)	51 (42.9)
70	3 (4.2)	4 (7.0)	4 (8.7)	6 (9.7)	7 (6.0)	10 (8.4)
60	1 (1.4)	0	1 (2.2)	0	2 (1.7)	0
50	0	0	1 (2.2)	0	1 (0.9)	0
Missing	0	0	0	1 (1.6)	0	1 (0.8)
Anatomical location of lesion, *n* (%)[a]						
Lung	17 (23.9)	20 (35.1)	19 (41.3)	16 (25.8)	36 (30.8)	36 (30.3)
Distant lymph node	19 (26.8)	18 (31.6)	13 (28.3)	13 (21.0)	32 (27.4)	31 (26.1)
Regional lymph node	7 (9.9)	8 (14.0)	6 (13.0)	6 (9.7)	13 (11.1)	14 (11.8)
Liver	45 (63.4)	43 (75.4)	30 (65.2)	40 (64.5)	75 (64.1)	83 (69.7)
Pancreas	45 (63.4)	32 (56.1)	30 (65.2)	40 (64.5)	75 (64.1)	72 (60.5)
Peritoneum	20 (28.2)	15 (26.3)	8 (17.4)	17 (27.4)	28 (23.9)	32 (26.9)
Other	17 (23.9)	17 (29.8)	10 (21.7)	22 (35.5)	27 (23.1)	39 (32.8)
CA19-9, *UlmL*						
Median	1423.0	308.0	831.0	5754.0	1278.0	1292.0
Range	7–499,311	7–100,145	7–178,143	7–873,326	7–499,311	7–873,326
Baseline albumin, *gldL*						
Median	4.1	4.1	4.0	3.9	4.1	4.0
Range	2.6–5.1	3.1–5.0	3.0–4.8	2.4–4.9	2.6–5.1	2.4–5.0

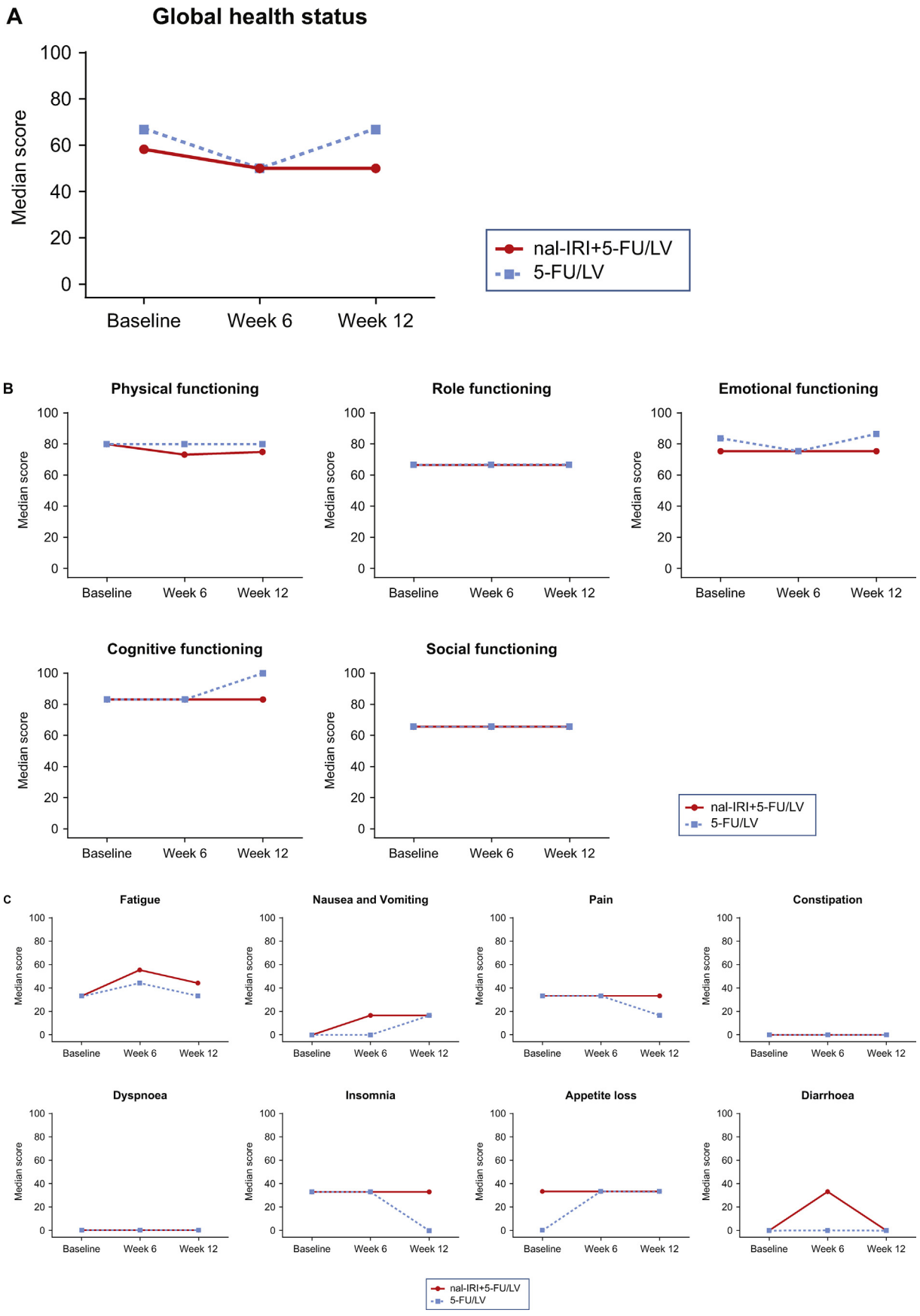
5-FU, 5-fluorouracil; ITT, intent-to-treat; LV, leucovorin; nal-IRI, liposomal irinotecan; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumours.

[a] Based on lesion locations followed for RECIST, v1.1. This includes all measurable and non-measurable lesions. This includes all metastatic and non-metastatic lesions. Subjects may be included in more than one category.

Table 2
Questionnaire completion over time in the PRO population.

Time point	nal-IRI+5-FU/LV (n = 71)			5-FU/LV (n = 57)		
	Patients on study, *n*	Patients with PRO data, *n*	Compliance rate, %	Patients on study, *n*	Patients with PRO data, *n*	Compliance rate, %
Baseline	71	71	100	57	57	100
Week 6	71	53	74.6	57	47	82.5
Week 12	63	49	77.8	44	30	68.2
Week 18	47	33	70.2	24	16	66.7
Week 24	36	23	63.9	16	9	56.3
Week 30	27	16	59.3	11	6	54.5
Week 36	17	3	17.6	5	3	60.0
Week 42	11	2	18.2	4	2	50.0
Week 48	7	2	28.6	3	3	100
Week 54	4	3	75.0	2	2	100
Week 60	2	0	0	2	2	100
Week 66	2	0	0	2	1	50.0

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; PRO, patient-reported outcome.


A
Global health status
Median score
100
80
60
40
20
0
Baseline
Week 6
Week 12
nal-IRI+5-FU/LV
5-FU/LV
B
Physical functioning
Role functioning
Emotional functioning
Cognitive functioning
Social functioning
C
Fatigue
Nausea and Vomiting
Pain
Constipation
Dyspnoea
Insomnia
Appetite loss
Diarrhoea

QLQ-C30 at baseline. HRQOL was evaluated in the PRO population (patients in the FPRO population who completed the baseline and at least one subsequent assessment on the EORTC QLQ-C30). Demographic and clinical variables of the PRO and ITT populations were compared for representativeness. Missing data patterns were analysed in the FPRO population. The primary endpoint of the NAPOLI-1 study was OS, and it was not powered for detecting differences in HRQOL, a secondary endpoint. Descriptive statistics are reported for the EORTC QLQ-C30 score and change (%) from baseline, by patient visit and by treatment arm. Response was classified by treatment arm. Duration of improvement was calculated for patients classified as improved.

Pairwise treatment group comparisons were performed on response classification for each subscale using Cochran–Mantel–Haenszel testing, and corresponding *P* values were presented. Adjusted *P* values were calculated using SAS PROC MULTTEST with false discovery rate option or equivalent algorithm. SAS software for Windows (v9.2 or higher) was used for all analyses. The cut-off date for this study was the same as for the pivotal analysis [15].

3. Results

3.1. Patient characteristics and EORTC QLQ-C30 completion and compliance

In the nal-IRI+5-FU/LV and 5-FU/LV arms, 210 patients (89% of the ITT population) completed the EORTC QLQ-C30 at baseline and comprised the FPRO (Fig. 1). One hundred twenty-eight patients (54.2% of the ITT population) completed the EORTC QLQ-C30 at baseline and at least one subsequent time point and comprised the PRO population. Of the remaining 108 patients (45.8% of the ITT population) not included in the PRO population (non-PRO population), most progressed rapidly, making participation difficult. Within the PRO population, 71 patients received nal-IRI+5-FU/LV and 57 received 5-FU/LV. Baseline characteristics were generally balanced across both arms (Table 1) and were similar to the overall study population, taking into consideration unplanned analyses of subgroups with limited patient numbers. Median age of patients in both arms was 63 years. The majority (77.5%–79%) of patients in both arms had a KPS of 80 or 90.

The EORTC QLQ-C30 questionnaire completion rate remained high in the nal-IRI+5-FU/LV (77.8%) and 5-FU/LV (68.2%) arms until week 12 (Table 2, Supplementary Table 1). Beyond week 12, PROs decreased over time, with only two patients remaining on study in each arm at week 66. As such, this report focusses on HRQOL until week 12. Compliance decreased slightly from baseline to week 12 in both arms and was similar across domains (Supplementary Table 2).

3.2. HRQOL scores at baseline and on treatment

With nal-IRI+5-FU/LV, the median global health status decreased 8.3 points at week 6 and remained there through week 12. In the 5-FU/LV control arm, global health status decreased 16.7 points at week 6 but returned to baseline at week 12 (Fig. 2 and Table 3).

There were few changes in functional domains. With nal-IRI+5-FU/LV, physical functioning decreased from 80.0 to 73.3 points at week 6 and was 75.0 points at week 12. With 5-FU/LV, cognitive functioning gained 16.7 points at week 12.

More changes occurred in symptom subscales. With nal-IRI+5-FU/LV, median fatigue score increased from 33.3 to 55.6 points at week 6 and was 44.4 at week 12. With 5-FU/LV, the median fatigue score increased from 33.3 to 44.4 points at week 6 but returned to baseline at week 12. Median nausea and vomiting score increased 16.7 points from baseline at week 12 in both arms. Median pain score remained at 33.3 points through week 12 in the nal-IRI+5-FU/LV arm but decreased from 33.3 points to 16.7 points at week 12 in the 5-FU/LV arm. Median dyspnoea and constipation scores remained at 0 points through week 12 in both arms. In the nal-IRI+5-FU/LV arm, median diarrhoea score increased from 0 to 33.3 at week 6 but returned to 0 at week 12. In the 5-FU/LV arm, median diarrhoea score remained at 0 points throughout. Overall at week 12, the nal-IRI+5-FU/LV arm had higher insomnia and financial difficulties scores than the 5-FU/LV arm (33.3 vs 0), but the appetite loss score was 33.3 in both arms.

For the fatigue scale, there was a median change from baseline of +11.1 and 0 in the nal-IRI+5-FU/LV arm and 5-FU/LV arm, respectively, at weeks 6 and 12, indicating a deterioration (Supplementary Table 3). In the pairwise group comparison of the nal-IRI+5-FU/LV and 5-FU/LV arms, small, albeit non-significant variations were observed in improvement or deterioration of global health and functional (Supplementary Fig. 1A) status or symptom scales (Supplementary Fig. 1B). These variations on individual scales did not translate into a significant overall deterioration.

Fig. 2. Median EORTC QLQ-C30 scores from baseline to week 12 in (**A**) global health status, (**B**) functional scales, and (**C**) symptom scales. A high score for the global health status or functional scales represents a high HRQOL, and an increase in scores represent an improvement in HRQOL, whereas a high score on the symptom scales represents low QOL, and an increase in scores represents deterioration in HRQOL. 5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; HRQOL, health-related quality of life; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer QOL core questionnaire C30.

Table 3
Patient HRQOL questionnaire score by domain.

	nal-IRI+5-FU/LV (n = 71) Median (range)						5-FU/LV (n = 57) Median (range)					
	Baseline		Week 6		Week 12		Baseline		Week 6		Week 12	
	Median	IQR, Q1,Q3	Median	IQR, Q1,Q3	Median	IQR, Q1,Q3	Median	IQR, Q1,Q3	Median	IQR, Q1,Q3	Median	IQR, Q1,Q3
Global health status	58.3	33.3, 66.7	50.0	33.3, 66.7	50.0	33.3, 66.7	66.7	50.0, 75.0	50.0	25.0, 75.0	66.7	50.0, 83.3
Functional scales												
Physical functioning	80.0	66.7, 93.3	73.3	53.3, 86.7	75.0	60.0, 93.3	80.0	66.7, 93.3	80.0	46.7, 93.3	80.0	66.7, 93.3
Role functioning	66.7	50.0, 100	66.7	41.7, 100	66.7	33.3, 100	66.7	33.3, 100	66.7	33.3, 100	66.7	50.0, 100
Emotional functioning	75.0	58.3, 91.7	75.0	66.7, 83.3	75.0	66.7, 83.3	83.3	66.7, 91.7	75.0	50.0, 91.7	86.1	58.3, 100
Cognitive functioning	83.3	66.7, 100	83.3	66.7, 100	83.3	66.7, 100	83.3	83.3, 100	83.3	66.7, 100	100.0	66.7, 100
Social functioning	66.7	50.0, 100	66.7	50.0, 100	66.7	50.0, 83.3	66.7	50.0, 100	66.7	33.3, 100	66.7	50.0, 100
Symptom scales												
Fatigue	33.3	22.2, 55.6	55.6	33.3, 66.7	44.4	22.2, 66.7	33.3	11.1, 55.6	44.4	22.2, 88.9	33.3	22.2, 55.6
Nausea and vomiting	0	0.0, 16.7	16.7	0.0, 33.3	16.7	0, 33.3	0	0.0, 16.7	0	0, 33.3	16.7	0, 33.3
Pain	33.3	16.7, 66.7	33.3	0, 50.0	33.3	0, 50.0	33.3	16.7, 50	33.3	0, 66.7	16.7	0, 33.3
Dyspnoea	0	0, 33.3	0	0, 33.3	0	0, 33.3	0	0, 33.3	0	0, 33.3	0	0, 33.3
Insomnia	33.3	0, 66.7	33.3	0, 33.3	33.3	0, 50.0	33.3	0, 33.3	33.3	0, 66.7	0	0, 33.3
Appetite loss	33.3	0, 66.7	33.3	0, 66.7	33.3	0, 66.7	0	0, 33.3	33.3	0, 66.7	33.3	0, 33.3
Constipation	0	0, 33.3	0	0, 33.3	0	0, 33.3	0	0, 33.3	0	0, 33.3	0	0, 33.3
Diarrhoea	0	0, 33.3	33.3	0, 33.3	0	0, 33.3	0	0, 0	0	0, 33.3	0	0, 33.3
Financial difficulties	33.3	0, 33.3	33.3	0, 33.3	33.3	0, 33.3	0	0, 33.3	0	0, 33.3	0	0, 33.3

5-FU, 5-fluorouracil; IQR, interquartile range; LV, leucovorin; nal-IRI, liposomal irinotecan; QoL, quality of life.

The median duration of improvement for global health status, physical, role and emotional functioning was numerically longer with the nal-IRI+5-FU/LV combination than with 5-FU/LV control (Table 4), but median duration of improvement for cognitive functioning was similar in both arms. Among the symptom scales, median duration of improvement for fatigue, nausea and vomiting, pain, and diarrhoea was shorter with the nal-IRI+5-FU/LV combination compared with 5-FU/LV control. Conversely, the median duration of improvement of dyspnoea, insomnia, and appetite loss was longer in the nal-IRI+5-FU/LV combination arm than in the 5-FU/LV control arm. Overall, more domains had longer improvements in the nal-IRI+5-FU/LV arm than in the 5-FU/LV arm, but these changes were not statistically significant.

Table 4
Duration of improvement, days.[a]

	nal-IRI+5-FU/LV (n = 71)	5-FU/LV (n = 57)
	Median (range)	Median (range)
Global health status	61 (43–287)	43.0 (43–168)
Functional scales		
Physical functioning	101 (43–282)	84 (43–168)
Role functioning	85 (43–282)	46.5 (43–128)
Emotional functioning	88.5 (43–282)	52.0 (43–128)
Cognitive functioning	88.5 (43–282)	88.5 (50–128)
Social functioning	55.0 (43–282)	68 (42–92)
Symptom scales		
Fatigue	74.5 (43–282)	86.0 (42–175)
Nausea and vomiting	107.0 (42–287)	224.5 (76–373)
Pain	92.0 (42–282)	107.0 (81–175)
Dyspnoea	155 (92–282)	85.0 (50–128)
Insomnia	127.0 (43–282)	93.0 (43–204)
Appetite loss	137 (50–287)	43.0 (43–50)
Constipation	113.0 (43–282)	109.0 (93–125)
Diarrhoea	127.5 (52–282)	167.5 (160–175)
Financial difficulties	99.0 (85–282)	–[b]

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a] Duration of improvement was summarised for patients who were classified as improved. Duration of improvement: if a patient achieves response more than once, with a return to baseline or worsening between responses, the longest duration was used as the duration of improvement.
[b] No patient in the 5-FU/LV arm was classified as improved.

3.3. Missing data analysis

The PRO population was representative of the ITT population (Table 1). In the FPRO population, the majority of the missing data exhibited the monotone missing pattern and was slightly higher with nal-IRI+5-FU/LV from week 18 onwards (Supplementary Table 4). Intermittent missingness was infrequent in both arms (0%–7.3%) and was slightly higher with nal-IRI+5-FU/LV. The most frequently recorded known reason of monotone missingness was disease progression, which was lower with nal-IRI+5-FU/LV (16.7%) than with 5-FU/LV (25%) (Supplementary Table 5).

4. Discussion

Pancreatic ductal adenocarcinoma is aggressive, and disease progression can significantly deteriorate

HRQOL [2,8]. Life expectancy for patients with mPDAC is typically less than 1 year [3]. Thus, preservation of HRQOL on treatment is particularly important. Yet, few studies in mPDAC report HRQOL data [19,24].

nal-IRI+5-FU/LV significantly improves median OS vs 5-FU/LV alone [15]. This analysis shows that patients had no substantial deterioration from baseline in most HRQOL subscales. The only differences from baseline between the nal-IRI+5-FU/LV combination and 5-FU/LV control therapy were a lower physical functioning score (−6.7) and a higher fatigue score (+11.1) with nal-IRI+5-FU/LV. Patients subjectively assessed these changes as 'minor' for physical function and 'moderate' for fatigue [21].

In a *post-hoc* analysis of the NAPOLI-1 study, using the quality-adjusted time without symptoms or toxicity (Q-TWiST) methodology, nal-IRI+5-FU/LV provided a relative gain of 24% compared with 5-FU/LV [25], exceeding the 15% difference threshold considered clinically meaningful [26].

The present HRQOL findings complement the Q-TWiST results and the previously reported survival benefit [15], suggesting that nal-IRI+5-FU/LV also maintains HRQOL in patients whose disease has progressed on a prior gemcitabine-based regimen, despite the addition of an active chemotherapy agent. HRQOL assessments have seldom been reported in pancreatic cancer trials, both in first-line or second-line settings [19,24,27]. This may be because poorly controlled mPDAC has a high symptom burden. The PRODIGE 4 study, which evaluated FOLFIRINOX versus gemcitabine in the first-line setting, showed that FOLFIRINOX improved OS and HRQOL, despite the increased toxicity of the FOLFIRINOX regimen, although this study had a notable patient attrition rate [28]. Two earlier interventional studies in other chemotherapy combinations in the second-line setting, however, either did not report HRQOL (CONKO-003) or found no significant change between treatment arms (PANCREOX) [19,27].

In this study, the EORTC QLQ-C30 questionnaire compliance rate was high until week 12 of treatment, after which the frequency of missing or incomplete data increased. The vast majority of missing data were explained by terminal missingness, the most frequent reason being progressive disease. This is consistent with other reports in mPDAC and reflects patient attrition typically observed in end-stage cancer studies [19,28,29]. As patients discontinued the study, EORTC QLQ-C30 compliance decreased. A more frequent HRQOL assessment may have increased data capture. It is unclear whether the improvements in HRQOL at week 12 were due to selection of patients with better HRQOL via attrition of patients with worsened QoL at week 6. It would be expected for this to be noted particularly with 5-FU/LV alone, as treatment discontinuation and progression were observed earlier in this arm [15]. Another reason could be general amelioration of side-effects over time [30]. HRQOL improvements could also be due to adequate dose reductions and supportive measurements, improvement of disease symptoms via treatment of side-effects, or a combination of all these factors. Other study limitations include a potential reporting bias because of the open-label design of the NAPOLI-1 study and a limited power to detect significant HRQOL differences between the two treatment arms. Additionally, the EORTC QLQ-C30 is a general questionnaire and may have failed to capture all nuances of mPDAC. Despite these limitations, this study provides randomised trial data on HRQOL, an important clinical insight.

5. Conclusions

The combination of nal-IRI+5-FU/LV significantly and clinically meaningfully extends median OS compared with 5-FU/LV alone without compromising HRQOL in patients with mPDAC that progressed on prior gemcitabine-based therapy. This dual benefit supports the nal-IRI+5-FU/LV regimen as a favourable treatment option for such patients with mPDAC.

Conflict of interest statement

Richard A. Hubner reports an advisor role for Celgene and Shire. Jean-Frédéric Blanc reports an advisor role for Baxalta (now part of Shire) and Shire. Davide Melisi reports research funding from Shire, Incyte and Celgene and a consulting role with Baxter, Eli Lilly, Incyte and Shire. Daniel D. Von Hoff reports research funding from Merrimack Pharmaceuticals during the conduct of the study and consulting fees from AlphaMed Consulting, outside the submitted work. Andrea Wang-Gillam reports an advisor role for Merrimack Pharmaceuticals and Ipsen. Li-Tzong Chen reports honoraria from Eli Lilly, Novartis, Bristol-Myers Squibb, Ono Pharmaceutical, TTY Biopharm, PharmaEngine, MSD, AstraZeneca, Syncore Bio, Five Prime and Ipsen; a consultant or advisor role for Eli Lilly, Novartis, Bristol-Myers Squibb, Ono Pharmaceutical, PharmaEngine, MSD, Five Prime and AstraZeneca; and research funding from Novartis, Merck Serono, TTY Biopharm, SynCoreBio, Polaris, Celgene and Pfizer. Khalid Mamlouk was employed by Merrimack Pharmaceuticals and reports a consultant role for Ipsen Biopharmaceuticals. Bruce Belanger was employed by Merrimack Pharmaceuticals and is currently an employee of Ipsen Bioscience. Yoojung Yang is an employee of Vertex Pharmaceuticals, and Shire and Vertex Pharmaceuticals stockholder. Floris A. de Jong is currently employed by Servier, was an employee of Shire at the time of study, and has stock or ownership

interests in Shire. Jens T. Siveke reports an advisor role for Baxalta (now part of Shire), Celgene, Roche, and Shire; honoraria from Shire and Celgene, and research funding from 4SC, Celgene, Bristol-Myers Squibb, and Roche. The other authors declare that they have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.09.029.

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